

-1-

SUBLINGUAL ADMINISTRATION OF NON-STEROIDAL
ANTI-INFLAMMATORY PHARMACOLOGICAL SUBSTANCES

* * * * *

DESCRIPTION

5 The present invention relates to a sublingual
administration method of non-steroidal anti-
inflammatories substances, referred as FANS
hereinafter, which allows to considerably reduce its
therapeutic dose, with the additional advantage of
10 increasing the quickness of the effects and improving
the tolerability.

FANS are drugs diffusely used for the control of
inflammatory symptoms of different type, generally
associated with pain and fever.

15 The oral administration, in the form of preparations
to swallow, is the more common. It presents, however,
some drawbacks which concern, in a more or less
evident way, all this class of drugs.

Firstly, it is known that FANS may produce injury to
20 the gastrointestinal system, consisting in ulcers,
erosions and haemorrhages (Gabriel et al., 1991). This
phenomenon is partly due to the central action
mechanism of FANS, the same which also explains the
anti-inflammatory properties thereof (Roberts and
25 Morrow, 2001), partly to a contact action, which
locally occurs on the gastrointestinal wall with which
these drugs contact after being swallowed.

The damages of the first type declared themselves
after the systemic absorption and are independent on
30 the route of administration, while those of the second
type precede the absorption and are bound to the oral
administration.

Studies on animals and humans shown that the oral
administration significantly contributes to the onset
35 of these side effects. In rats, some FANS cause

-2-

gastrointestinal lesions significantly more serious by oral way than after parenteral administration (Pfeiffer and Lewandowski, 1971; Cioli et al., 1979). The same phenomenon has been observed in humans and is explained in that, after oral administration, the FANS directly contact the gastrointestinal mucosa: in this way, their toxic local effects are added to those performed after the systemic absorption (Bjarnson and Thjodleifsson, 1999; Roberts and Morrow, 2001).

Another unfavourable aspect of the oral administration is to involve a first passage through the liver; consequently, FANS reach high concentrations in this organ, with a formation of reactive metabolites which can produce an oxidative stress and cause mitochondrial damages. In sensitive persons (metabolic idiosyncrasy), hepatotoxic reactions, serious as well, may result (Boesterli, 2002).

In order to reduce the drawbacks connected to the oral administration, FANS may be administered in gastro-resistant formulations, which do not deliver the active substance in the stomach. In this way, the gastric tolerability is improved but the erosions due to the direct contact of the active substance with the intestinal mucosa are not avoided, which can be equally dangerous (Davies, 1999). Further, FANS may be administered by injection and transdermically. In this way, the contact effect at the gastric and intestinal level may be avoided and the first passage through the liver is eliminated, thus being able to mitigate the hepatotoxic effects. Both these routes of administration, however, present drawbacks, which must be kept in mind (Wilkinson, 2001).

The injective route obliges to maintain the asepsis, may cause pain and makes the self-medication difficult.

-3-

The transdermic route is not always usable because of dosage problems and involves a slow absorption, hardly compatible with the treatment of acute inflammatory conditions, which need treatments promptly effective; few drugs, moreover, easily enter through the intact skin.

Finally, another possibility is offered by the rectal route, which however involves a rather irregular absorption and may irritate the mucosa of the last tract of the intestine; further, it reduces but it does not eliminate the effect of the first passage in the liver (Wilkinson, 2001).

Therefore, so far the sublingual administration of non-steroidal anti-inflammatory substances has never been subject of study or investigation.

Surprisingly, the above mentioned drawbacks are overcome through the sublingual administration of FANS, since from the oral cavity the drugs directly reach the superior vena cava, in this way the local component of the gastrointestinal damaging action is eliminated and the first massive passage through the liver is avoided.

The sublingual administration allows to considerably reduce the therapeutic dose, with respect to an oral formulation containing the same anti-inflammatory agent, with the advantage of increasing the quickness of the effects and ameliorating the tolerability. Further, the sublingual administration is easy to carry out.

The above mentioned advantages appeared by using, through sublingual administration, various active substances representative of the whole class of FANS, such as, for instance, nimesulide.

Nimesulide, as it is known, is particularly effective in the acute forms associated with pain. Its use,

-4-

however, may cause adverse reactions to the gastrointestinal tract and, most of all, to the liver (REFI 2000).

5 In the performed experimentation, the used sublingual preparations consisted of tablets which can be separated in two parts.

During this experimentation, it unexpectedly emerged that the sublingual administration of FANS allows to remarkably reduce the therapeutic dose necessary for
10 obtaining the desired anti-inflammatory effect.

The experimentation has further been closely examined, both by treating in the following period the same patients with the traditional oral preparation and with the sublingual one, and by
15 comparing groups of patients treated with the two methods. Besides allowing to considerably reduce the therapeutic dose, the sublingual administration presents the additional advantage of improving the quickness of the effects, which in the acute
20 inflammatory conditions is of great importance, and the tolerability of FANS. The relative ascertainment to the dosage reduction required for obtaining a complete therapeutic effect was never been pointed out in the prior art.

25 Advantageously, the excipients used for the sublingual preparations of the tested FANS have been carefully selected among the available excipients in the pharmaceutical art.

The best excipients have proved to be those promoting
30 the delivery of the active substance, by reducing the possible risk of local lesions for the oral mucosa which is exposed to the direct contact with the FANS.

By using such types of excipients, during the experimentation carried out on patients, injuries of
35 the type above mentioned have never been pointed out.

-5-

By way of example only, (Example 1), a tested preparation showed the following excipients composition:

| | | |
|----|----------------------------|----------|
| | Nimesulide | mg 100.0 |
| 5 | Mannitol | mg 200.0 |
| | Sodium saccharate | mg 30.0 |
| | Microcrystalline cellulose | mg 100.0 |
| | PEG 6000 powder | mg 5.0 |
| | Citric acid | mg 30.0 |
| 10 | Magnesium stearate | mg 20.0 |
| | Mint flavouring | mg 20.0 |

By way of example only, (Example 2), another tested preparation showed the following excipients composition:

| | | |
|----|----------------------------|----------|
| 15 | Nimesulide | mg 50.0 |
| | Mannitol | mg 100.0 |
| | Sodium saccharate | mg 5.0 |
| | Microcrystalline cellulose | mg 50.0 |
| | PEG 6000 powder | mg 2.5 |
| 20 | Citric acid | mg 25.0 |
| | Magnesium stearate | mg 5.0 |
| | Mint flavouring | mg 10.0 |

The patients seem to prefer the tablets of smaller sizes, but the reasons seem to be psychological only, as from the point of view of the therapeutic dosage reduction, the quickness of the effects and the tolerability, the size of the tablets and their formulations has not been influential. The reduction of the therapeutic dosage seems to depend, therefore, more from the route of administration than the formulation of the preparation, even if, of course, an influence of this latter cannot be excluded.

Greater advantages can be obtained by using tablets capable of quickly disintegrating, as the absorption of FANS is facilitated and the risk of local lesions

-6-

is reduced.

All the sublingual preparations used in the experimentation are characterized by a prompt disintegration.

5 The experimentation has involved several FANS, such as, for example ketoprofen, nimesulide, naproxen and ibuprofen.

Moreover, other FANS provided with unusual physical-chemical features have been taken into consideration,
10 such as, for instance, paracetamol, ketorolac, tenoxicam and diclofenac.

The present invention also applies to the 2-cyclo-oxygenase inhibitors, such as celecoxib and rophcoxib, with the advantage of a higher quickness
15 of the therapeutic effects.

The experimentation carried out with the ketoprofen, the nimesulid and the ibuprofen on one hand, and with the paracetamol and diclofenac on the other hand, leads to consider that the observed reduction of the
20 therapeutic dosage depends on the sublingual administration itself rather than the specific features of each drug.

A first group of patients subjected to the experimentation showed a clinical anamnesis of peptic
25 ulcer or, in a more general sense, intolerance to the oral preparations of FANS. Afterward, the experimentation has been extended also to patients which well tolerated the traditional oral administration, by pointing out that also in those
30 people the sublingual administration allows a drastic reduction of the therapeutic dose with respect to an oral formulation containing the same anti-inflammatory agent.

In order to more specifically show the invention, the
35 following non limitative examples of galenical

-7-

formulations are reported:

By way of example only, (Example 3), another experimented preparation showed the following composition:

| | | | |
|----|----------------------------|----|------|
| 5 | Ketoprofen | mg | 25.0 |
| | Mannitol | mg | 50.0 |
| | Sodium saccharate | mg | 5.0 |
| | Microcrystalline cellulose | mg | 25.0 |
| | PEG 6000 powder | mg | 2.5 |
| 10 | Citric acid | mg | 12.5 |
| | Magnesium stearate | mg | 3.0 |
| | Mint flavouring | mg | 5.0 |

By way of example only, (Example 4), another experimented preparation showed the following

15 composition:

| | | | |
|----|----------------------------|----|-------|
| | Ibuprofen | mg | 100.0 |
| | Mannitol | mg | 125.0 |
| | Sodium saccharate | mg | 5.0 |
| | Microcrystalline cellulose | mg | .75.0 |
| 20 | PEG 6000 powder | mg | 2.5 |
| | Citric acid | mg | 25.0 |
| | Magnesium stearate | mg | 5.0 |
| | Mint flavouring | mg | 10.0 |

25 In general, the formulation according to the invention may be in a pharmaceutical form selected among: gel, granulate, powder, freeze-dried product, pressed capsule or pill.

Further, the pharmaceutical formulation according to the invention may include a water soluble excipient and/or a crystalline water insoluble excipient having a disintegrating function.

30 For instance, the water soluble excipient is the mannitol; the crystalline water insoluble excipient having a disintegrating function is the
35 microcrystalline cellulose.

-8-

Moreover, the pharmaceutical formulation according to the invention may include: a lubricant, preferably said lubricant is the magnesium stearate and/or the PEG 6000 powder; a sweetener, preferably said
5 sweetener is the sodium saccharate.

Of course, the common co-formulations usually used in the pharmaceutical technology may be employed without any limitation.

Finally, the formulations according to the invention
10 are prepared according to the known teachings and the methods generally employed in the field.

Some mentioned references are reported hereinafter:

1.Bjarnason I., Thjodleifsson B.

Gastrointestinal toxicity of non-steroidal anti-
15 inflammatory drugs: the effect of nimesulide compared with naproxen on the human gastrointestinal tract, Rheumatology 1999 May, 38 Suppl 1: 24-32.

2.Boelsterli U.A.

Mechanisms of NSAID-induced hepatotoxicity: focus on
20 nimesulide, Drug Saf, 2002, 25 (9): 633-648.

3.Cioli V., Putzolu S., Rossi V., Scorza Barcellona P., Corradino C.

The role of direct tissue contact in the production of gastrointestinal ulcers by anti-inflammatory drugs in
25 rats, Toxicol. Appl. Pharmacol. 1979 Sep 15; 50 (2): 283-289.

4. Gabriel S.E., Jaakkimainen L., Bombardier C.

Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory
30 drugs. A meta-analysis, Ann Intern Med 1991 Nov 15, 115 (10): 787-796.

5.Davies N.M.

Sustained release and enteric coated NSAIDs: are they really GI safe?, Pharm Pharm Sci 1999 Jan-Apr; 2 (1):
35 5-14.

-9-

6. Roberts II L.J., Morrow J.D.
Analgesic-antipyretic and antiinflammatory agents and
drugs employed in the treatment of gout, in Goodman
and Gilman's, The pharmacological basis of
5 therapeutics, 10th edition, eds. Hardman J.G. and
Limbird L.E., 2001, McGraw-Hill, pag. 687-731.
7. Pfeiffer C. J., Lewandowski L.G.
Comparison of gastric toxicity of acetylsalicylic acid
with route of administration in the rat, Arch. Int.
10 Pharmacodyn Ther. 1971 Mar; 190 (1): 5-13.
8. REFI (Repertorio Farmaceutico Italiano), 2000.
9. Wilkinson G.R.
The Dynamics of drug absorption, distribution, and
elimination, in Goodman and Gilman's, The
15 pharmacological basis of therapeutics, 10th edition,
eds. Hardman J.G. and Limbird L.E., 2001, McGraw-Hill,
pag. 3-29.